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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,335	09/22/2003	Francesco Borrelli	BORRELLI2A	8379

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,335	BORRELLI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In a telephone call to the Examiner by Alan Yun on 10/30/08, Mr. Yun indicated that the referernces submitted in February '08 are indeed present in the file. In view of this, finality is withdrawn, and prosecution reopened to allow consideration of those references.

Claim Status

Claims 20-24 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-24 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a TNF antagonist, does not reasonably provide enablement for a pharmaceutical composition comprising a TNF antagonist and either hCG, LH or FSH. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record. In addition, in reviewing the literature, the Examiner has determined that there are significant differences between mild to moderate endometriosis and severe endometriosis. The specification makes no distinction between the two, nor are there ANY working examples of the claimed invention. Therefore, there is no guidance as to the relative amounts of the active agents that should be used, nor how to use them; how they should be administered, and over what time periods. It is well known that use of FSH, LH and hCG can cause ovarian hyperstimulation. The effects of those hormones in combination with TNF inhibitors cannot be predicted, and would require

undue experimentation. Further, the composition would have to vary depending upon *how* the infertility was to be treated; whether the desired effect were merely ovarian stimulation (as is achieved with clomide), or ovarian hyperstimulation, as is practiced for *in vitro* fertilization.

Applicants traversal in the paper submitted 2/19/2008 has been fully considered but not deemed persuasive for reasons that follow:

Applicants argue that Adashi et al. teach that GnRHa has not been shown to enhanced fertility in patients with endometriosis. This argument has been fully considered but is not deemed persuasive because Adashi is drawn not to treatment of infertility, but to treatment of endometriosis. The compounds used were GnRH derivatives "with longer half-lives and greater receptor binding affinity. *The net results is downregulation of pituitary GnRH receptors and resultant "medical oophorectomy" from the hypogonadotropic state."* , e.g. a medical equivalent of removal of the ovaries, which would not be expected to increase fertility. Unlike the claims in which, *biologically* are being administered with TNF inhibitor, Adashi is discussing a situation in which an *inhibitor* of *active* FSH, LH, or hCG is administered, in the *absence of* a TNF inhibitor. Thus, the experiment described in Adashi does not apply to the instant claims.

Applicants point to De Hondt et al. as teaching that gonadotropins are known to be used to increase fertility in patients in combination with surgery associated with endometriosis. This is a well known fact, and stipulated by the examiner. The question here is whether it would have been predictable to the person of ordinary skill in the art *at the time the invention was made* (1999) that inhibition of TNF in concert with administration of gonadotrophic hormones would be expected to increase fertility in women suffering endometriosis. De Hondt does not support this assertion. De Hondt points to a paper published in 2004, five years after the effective filing date of this application, as suggesting that TNF production *might* be responsible for reduced fecundity in endometriosis patients. Accordingly, even five years *after* the effective filing date, this correlation had not been established. The remainder of the paper concerns fertility treatment in combination with *surgical* treatment of endometriosis, and has no bearing on the pending claims. Kemmann et al., which is drawn to ovarian stimulation to improver fertility in women with minimal/mild endometriosis (a limitation not found in the claims) after laser laparoscopy. Applicants have not pointed to any correlation between treatment of endometriosis with TNF inhibitors with treatment of such by surgical or laser laparoscopic means, accordingly the

references do not address the claimed invention, as the former involves anti-cytokine treatment, rather than mechanical treatment of endometriosis. The word TNF does not even occur in the Kemmann article. The same is true of the Goker article, which is a retrospective analysis of controlled ovarian hypertimulation and intrauterine insemination for infertility associated with endometriosis. No mention is made of TNF. The ONLY relevant teaching is at page 23, where it is suggested that "operative laparoscopy *with or without* gonadatrophin releasing hormone analog should be considered as the first-line therapy of endometriosis associated infertility" (emphasis added).

Thus, having considered the articles submitted, the Examiner does not find that there is any evidence therein that treatment with TNF inhibitors *in concert with* gonadotropins, would be successful, nor is there any suggestion of doing so, even years after the current filing date. Applicants are arguing that papers that involve the *surgical* removal of endometrial tumors are probative of results expected with administration of TNF inhibitors, a presumption for which there is no scientific support or evidence. The mechanisms are completely different, as are the timelines for results (surgery being immediate, anti-TNF administration taking longer), and thus one would not expect one to be predictive of the other. Given the unpredictable nature of treatment of endometriosis, the unpredictable nature of infertility, the lack of an association between endometriosis and TNF, and the lack of predictability of anti-TNF therapy on conception and pregnancy, the Examiner maintains that undue experimentation would be required to determine how to practice the claimed invention, if it can be done at all.

The specification teaches at page 12:

The TNF antagonist can be administered prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, in particular for the treatment of infertility. TNF antagonists that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions. In particular, when infertility is the endometriosis associated disorder intended to be cured, biologically active human chorionic gonadotrophin (hCG), luteinizing hormone (LH) or follicle stimulating hormone (FSH), either in a natural highly purified or in a recombinant form, can be administered. The presumed

mechanism of administering the claimed composition would be that the anti-TNF molecule would shrink the endometrial tissue, and the hormones would stimulate ovulation.

However, there is no guidance as to how to co-administer the proteins to achieve the desired effect. Such determination would require undue experimentation, especially as applied to humans, who are clearly the intended subjects.

It is noted that the connection between TNF and endometriosis has been known for quite some time, as evidenced by applicant's own patent, 6,663,865. However, in addition to being an "unwanted" cytokine associated with endometriosis, it is also true that TNF plays a normal role in pregnancy; many stages of development of an embryo require selective cell *death*, which is or may be associated with TNF. For example:

Arend et al., Die medikamentose Behandlung der rheumatoiden Arthritis, Der Orthopade (Germany) Dec 2003, 32 (12) p1095-103, (abstract only enclosed) teach that in the treatment of rheumatoid arthritis, that administration of TNF inhibitors should be discontinued 6 months prior to conception.

Kochi et al., International journal of biochemistry (ENGLAND) Jan 1994, 26 (1) p111-9, teach that "Using the RT/PCR method, we examined mRNA expression of several inflammatory factors in mouse embryos during mid-late embryonal development. mRNAs of tumor necrosis factor (TNF)-alpha, TNF-beta, their receptors (TNF-RI, TNF-RII), transforming growth factor (TGF)-beta, were expressed constitutively in most of the embryonic tissues. " (See abstract). Even more importantly, Ohsawa et al., Developmental biology (UNITED STATES) Oct 1989, 135 (2) p459-61, report that ""We investigated the expression of the tumor necrosis factor (TNF)gene during development of mouse embryos, and observed its transient expression on Days 9 and 10 of gestation. We also detected a 25-kDa protein showing immunological cross-reactivity with mouse TNF antibody in an extract of 10-day embryos. These results suggest that TNF plays a role in mammalian ontogenesis."(Abstract.) This establishes that TNF has a role in early gestation, such that the co-administration of TNF inhibitors and gonadotrophins would have to be carefully investigated, the timing of administration to enhance fertility carefully determined, and might not be possible at all.

Thus, it remains that there are *no* reports in the art, either before or after the filing date, of the *simultaneous* treatment of endometriosis using anti-TNF agents and fertility using gonadotropins, the effects of doing so would be unpredictable, there are no reports in the art of doing so, and it would require undue experimentation (due to necessity of authorization by review boards, other ethical considerations, and inability to obtain volunteers for such studies, i.e. ethical considerations), to determine how to do so in humans, which are the ultimate subjects of this patent application. Accordingly, there is no enabled use for the claimed pharmaceutical compositions.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.
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Art Unit 1647